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**THIS APPLICATION IS THE ENTRY INTO THE
NATIONAL PHASE UNDER 35 U.S.C. 371**

Applicant(s): THE DOW CHEMICAL COMPANY

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Title: AMINOALKYLENEPHOSPHONATES FOR TREATMENT OF BONE DISORDERS

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AMINOALKYLENEPHOSPHONATES FOR TREATMENT OF BONE
DISORDERS

5 This invention relates to the use of
aminoalkylenephosphonates for treatment of bone disorders
such as osteoporosis.

This invention involves the use of
10 aminoalkylenephosphonates, such as, for example, 1,4,7,10-
tetraazacyclododecane-1,4,7,10-tetramethylenephosphonic
acid (DOTMP) and 3,6,9,15-tetraazabicyclo[9.3.1]tetradeca-
1(15),11,13-triene-3,6,9-trimethylenephosphonic acid
(PCTMP) for use in the inhibition of bone resorption.
15 This application is directed toward use in the prevention
and/or treatment of bone diseases such as osteoporosis.
Bone is a dynamic tissue, continually undergoing
remodeling. Hydroxyapatite, the main inorganic
constituent of bone, is constantly being deposited and
20 resorbed. In pathological states such as osteoporosis a
shift in the balance of these two processes occurs,
resulting in a net loss of mineralized tissue. This loss
results in impaired skeletal function and clinical
fractures. Osteoporosis is an enormous public health
25 problem affecting as many as 25 million people in the
United States alone. It is a pervasive disease that has
staggering costs to society in terms of morbidity,
mortality, and economics. As the population becomes more
aged, the magnitude of this problem will certainly become
30 greater.

Currently only three drugs - estrogen, calcitonin,
and alendronate are approved by the FDA for use in the
treatment of osteoporosis. Both estrogen and calcitonin
35 have some drawbacks (for example, estrogen - risk of
endometrial carcinoma, calcitonin - allergic reaction) and
are not always successful. The recently approved

bisphosphonate alendronate (4-amino-1-hydroxybutylidenebisphosphonate) is a member of a class of compounds that has received much attention for their potential in treating bone-related illnesses.

5

Bisphosphonates all contain the basic P-C-P structure. Examples such as etidronate (1-hydroxy-ethylidenebisphosphonate), risedronate [1-hydroxy-2-(3-pyridinyl)ethylenebisphosphonate], pamidronate (3-amino-1-hydroxypropylidenebisphosphonate), tiludronate (4-chlorophenylthiomethylenebisphosphonate) have already been approved for the treatment of a rare bone condition called Paget's disease.

15 Aminoalkylenephosphonates have not been investigated for these applications. It is known that these compounds have a strong affinity for bone (for example, EDTMP and DOTMP radiopharmaceutical bone agents) and have low soft tissue localization. They have unique properties such as
20 the ability to inhibit calcium phosphate scale formation at very low concentrations.

It has now been discovered that aminoalkylene-phosphonates can inhibit bone mineral density loss. In
25 fact, a screening study of various aminomethylene-phosphonates in an ovariectomized rat osteoporosis model has now shown that PCTMP is as good as, and may even be superior to, alendronate in its ability to inhibit bone mineral loss.

30

The present invention relates to a method for preventing or minimizing loss of bone mineral in mammals which method comprises administering to a mammal an amount of an aminoalkylenephosphonate which is effective to
35 prevent or minimize loss of bone mineral density.

In another aspect, the present invention relates to the use of an aminoalkylenephosphonate or a pharmaceutically acceptable salt thereof in the manufacture of a pharmaceutical formulation for preventing
5 or minimizing loss of bone mineral in mammals.

The term "aminoalkylenephosphonate" as used herein refers to those phosphonates and phosphonic acids which incorporate an amine moiety, whether aliphatic or cyclic,
10 attached via the amine nitrogen through an alkylene group to the phosphonate or phosphonic acid moiety. The aminoalkylenephosphonates of the present invention should have at least one $R-N(Alk-PO_3H_2)_2$ group or at least two $RR'-N-Alk-PO_3H_2$ groups wherein R and R' can be, same or
15 different, aliphatic or cyclic moiety, and Alk is an alkylene group having from 1 to 4 carbon atoms.

The amine moiety of the aminoalkylenephosphonates of the present invention represented by the $R-N=$ and $RR'-N-$ in
20 the aforementioned $R-N(Alk-PO_3H_2)_2$ and $RR'-N-Alk-PO_3H_2$ groups is derived from either an aliphatic or a cyclic polyamine in which hydrogen atoms bonded to the nitrogen atom(s) in the amine moiety are partially or completely substituted by an alkylphosphonate group. Non-limiting examples of the
25 amines suitable as amine moieties in the practice of the present invention are ethylenediamine (EDA), diethylenetriamine (DETA), triethylenetetraamine (TETA), 1,4,7,10-tetraazacyclododecane, 3,6,9,15-tetraza-bicyclo[9.3.1]tetradeca-1(15),11,13-triene, 2,11-diaza[3.3](2,6)pyridinophane, 2-(aminomethyl)pyridine,
30 2,6-bis(aminomethyl)pyridine.

The alkylene group having from 1 to 4 carbon atoms contemplated by Alk in the aforementioned formulas can be
35 straight or branched chain alkylene group. Non-limiting examples of such alkylene groups are methylene, ethylene,

propylene, isopropylene, and butylene. The preferred alkylene group is methylene ($-\text{CH}_2-$) group.

Preferred aminoalkylenephosphonates are
5 aminomethylenephosphonates. Particularly preferred aminoalkylenephosphonates are 1,4,7,10-tetraaza-cyclododecane-1,4,7,10-tetramethylenephosphonic acid (DOTMP), 3,6,9,15-tetraazabicyclo[9.3.1]tetradeca-
1(15),11,13-triene-3,6,9-trimethylenephosphonic acid
10 (PCTMP), N,N'-bis(methylenephosphonic acid)-2,11-diaza[3.3](2,6)pyridinophane (BP2MP) and N,N-bis(methylene phosphonic acid)-2-(aminomethyl)pyridine (AMPDMP).

The aminoalkylenephosphonates contemplated by the
15 present invention are well known in the art and numerous methods for their preparation have been disclosed. See, for example, U.S. Patent No. 3,288,846 (Irani et al) and U.S. Patent No. 4,898,724 (Simon et al), both incorporated herein by reference.

20 The aminoalkylenephosphonates of the present invention are used in an amount effective to prevent or minimize loss of bone mineral. The effective amount will vary depending on the mammal, aminoalkylenephosphonate
25 used and the method of its administration (for example, oral or parenteral). A person of ordinary skill in the art will know how to determine the effective amount of aminoalkylene-phosphonate.

30 The aminoalkylenephosphonates of the present invention can be administered to a mammal on a daily or weekly regiment basis. Typically, for average 50 kg mammal, the effective weekly parenteral dose is in the range of from about 0.01 mg to about 500 mg, preferably
35 from about 0.1 mg to about 250 mg, most preferably from about 0.1 to about 70 mg. Typically, for average 50 kg

mammal, the effective daily oral dose is in the range of from about 0.1 mg to about 40 g, preferably from about 0.1 mg to about 10 g, most preferably from about 0.1 to about 5 g.

5

In the practice of the present invention the aminoalkylenephosphonate may be administered per se or as a component of a pharmaceutically acceptable composition.

10 Thus, the present invention may be practiced with the aminoalkylenephosphonate being provided in pharmaceutical formulation, both for veterinary and for human medical use. Such pharmaceutical formulations comprise the active agent (the aminoalkylenephosphonate) together with one or
15 more pharmaceutically acceptable carriers thereof and optionally any other therapeutic ingredients. The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredient(s) in the formulation and not unsuitably deleterious to the
20 recipient thereof. The aminoalkylenephosphonate is provided in an effective amount, as described above, and in a quantity appropriate to achieve the desired dose.

 The formulations include those suitable for oral,
25 rectal, topical, nasal, ophthalmic, or parenteral (including subcutaneous, intramuscular, and intravenous) administration. Formulations may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing the aminoalkylenephosphonate
30 into association with a carrier, which constitute one or more accessory ingredients. In general, the formulation may be prepared by uniformly and intimately bringing the aminoalkylenephosphonate into association with a liquid carrier, a finely divided solid carrier, or both, and
35 then, if necessary, shaping the product into desired formulation. In addition, the formulations of this

invention may further include one or more accessory ingredient(s) selected from diluents, buffers, flavoring agents, binders, disintegrants, surface active agents, thickeners, lubricants, preservatives.

5

The following Examples are provided to illustrate the present invention, and should not be construed as limiting thereof.

10 Example 1

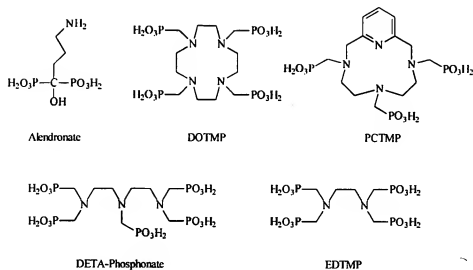
Eleven week old Female Sprague-Dawley laboratory rats (75) were fed a commercial rat diet and were allowed to drink water ad libitum. They were housed in pairs in an air-conditioned environment, and were allowed to enjoy 14 hours of illumination per day. Ten rats were sham-operated and were used as "non-osteopenic" control rats. All of the other rats were ovariectomized at 12 weeks of age. All surgeries were done under injectable anesthesia. Ten of the ovariectomized rats were used as an "osteopenic but non-treated" control, and did not receive any phosphonate treatments. The remaining rats were given various phosphonate compounds in groups of ten.

25 Phosphonates (5 mg/kg) were administered subcutaneously (to insure better bioavailability). The rats were given doses three times during the first week and once a week thereafter.

30 Structures of the compounds tested are shown below in Figure 1.

Figure 1. Structures of Compounds Tested (Example 1)

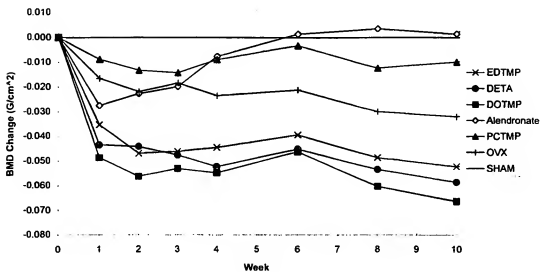
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10 Bone mineral density was determined by single photon absorptiometry while the rats were under injectable anesthesia. The distal femoral metaphysis of all rats were scanned at weekly intervals for ten weeks.

15 Figure 2 below shows the average drop in bone mineral density, normalized to the sham-operated control group, for the ovariectomized (OVX) control group and for the treatment groups.

Figure 2. Average Change in BMD
(Normalized to sham-operated control = 0)



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As can be seen, relative to the sham-operated control, the OVX group loses bone mineral density (BMD) over time. Three aminomethylenephosphonates, DOTMP, EDTMP, and DETA-Phosphonate, all lost more BMD than the OVX group (at this dose level). Both the alendronate and PCTMP groups maintained BMD. (Because of the difference in molecular weight, PCTMP was actually used at a lower dose level than alendronate on a mole basis.)

By week 10, there are three statistical groupings. The sham operated controls, alendronate, and PCTMP are all statistically equivalent. The ovariectomized controls are in a group by themselves, as are the other three aminomethylenephosphonates.

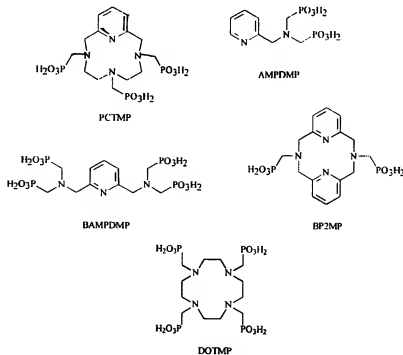
Example 2:

A second study was undertaken to explore the effect of structural changes in PCTMP. The structures of the compounds tested are shown below in Figure 3. Included in the study was DOTMP at one tenth the dose, that is, 0.5 mg/kg. All other compounds were dosed at 5 mg/kg. In this study, bone mineral density was determined by dual energy X-ray absorptiometry (DEXA). Other aspects of the study were substantially the same as in Example 1. The results of the study are shown in Figure 4 below.

Again, it can be seen that, relative to the sham-operated controls, the OVX control group lost significant BMD over the study period. As before, PCTMP shows an improvement over the OVX group. AMPDMP and BP2MP both look even better, but the best compound tested was DOTMP at 0.5 mg/kg. At this dose level it was equivalent to the sham-operated control.

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Figure 3. Structures of Compounds Tested



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Figure 4. Average Change in BMD
(Normalized to sham-operated control = 0)

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